REMARKS

Claims 23-42 are now pending for prosecution in this case. As submitted herewith, Claims 1-22 are cancelled and Claims 23-42 are added.

An amendment was filed on August 3, 2001 in the parent application, USSN 09/383,667, to which the Examiner responded with a 5-way restriction on Oct. 19, 2001, to which Applicants further elected Group I, which ultimately culminated in a notice of allowance mailed on April 9, 2003. The Examiner essentially grouped the claims on the basis of the subject matter comprehended by the CDRs. While the claims of the parent application were directed to nucleic acid encoding antibodies, those of the present application are directed to the antibodies themselves, and the compositions and articles of manufacture comprising them. Since the Examiner has already found the nucleic acid encoding such antibodies patentable, it is expected that the antibodies themselves would also be patentable.

Support for the above claim amendments appears in the specification at least as follows:

Claim 23: Generally at page 17, line 23 through page 19, line 29; Figure 2 and page 21, line 14 through page 24, line 2. Support for binding to a factor IX/IXa Gla domain at page 2, lines 29-31; page 6, lines 1-6 (Figure 3). Support for specific binding at page 7, lines 1-10 (Figures 6A-6B); page 13, lines 26-29; page 14, line 30 to page 15, line 7; and page 57, lines 7 to page 59, line 7.

Claim 24: Page 51, lines 9-10.

Claim 25: Page 50, line 30; page 51, line 9.

Claim 26: Page 51, lines 24-25.

Claims 27-31: Page 49, line 21 through page 50, line 3.

Claims 32-35: Page 50, lines 16-17.

Claims 36-42: Page 4, line 8-20, and as described for depending claims.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

No new matter has been introduced, and entry of these amendments is respectfully requested.

The examiner is invited to contact the undersigned at (650) 225-1489 in order to expedite the resolution of any remaining issues.

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The paragraph beginning at page 1, line 9 (immediately after the title) has been amended as follows:

The present application is a continuation of USSN 09/383,667, now allowed; which claims priority under 35 U.S.C. § 119 to provisional application numbers 60/122,767, filed March 3, 1999 and 60/098,233, filed August 28, 1998, both abandoned.

The paragraph beginning at page 1, line 30 has been amended as follows:

The Gla domain of FIX/FIXa contains important structural determinants for interaction with high affinity binding sites on vascular endothelial cells and platelets (Heimark et al., (1983) Biochem. Biophys. Res. Commun. 111:723-731; Ahmad et al., (1994) Biochem. 33:12048-12055; Ryan et al., (1989) J. Biol. Chem. 264:20283-20287; Toomey et al., (1992) Biochemistry 31:1806-1808; Cheung et al., (1992) J. Bio. Chem. 267:20529-20531; Rawala-Sheikh et al., (1992) Blood 79:398-405; Cheung et al., (1996) Proc. Natl. Acad. Sci. USA 93:11068-11073; ~~Prokok~~Prorok et al., (1996) Int. J. Pept. Prot. Res. 48:281-285; Ahmad et al., (1998) Biochemistry 37:1671-1679). In the presence of Ca++ and Mg++ the FIX/FIXa Gla domain adopts different conformations. Coagulation reactions, such as FIX/FIXa-mediated activation of FX proceed with high efficiency on the surface of activated platelets (Ahmad and Walsh (1994) Trends Cardiovasc. Med., 4:271-277).

The paragraph beginning at page 2, line 11 has been amended as follows:

Antibodies that bind the FIX/FIXa Gla domain have been shown to inhibit FIX/FIXa function, such as cell binding (Cheung et al., (1996) supra; clotting activity (Sugo et al., (1990) Thromb. Res. 58:603-614) and FIX/FIXa activation by FXI (Sugo et al., (1990) supra; ~~Leibman~~Liebman et al., (1987) J. Bio. Chem. 262:7605-7612). Rabbit and murine antibodies to FIX/FIXa have been shown to bind to the C- and N-terminal region of the Gla domain (Liebman et al., (1993) Eur. J. Biochem. 212:339-345 and Sugo et al., (1990) Thromb. Res. 58:603-614). Antibodies reactive with human FIX/IXa have been shown to inhibit the activation of FIX to FIXa and inhibit coagulation in a FIXa dependent assay (Blackburn et al., (1997) Blood

90:Suppl. 1:424a-425a). Active site inhibited FIXa attenuates thrombosis in vivo (Wong et al., (1997) Thromb. Haemost. 77:1143-1147; Benedict et al., (1991) J. Clin. Invest. 88:1760-1765; Spanier et al., (1998) ~~Am.~~ J. Thoracic Cardiovasc. Surgery 115:1179-1188).

The paragraph beginning at page 10, line 24 has been amended as follows:

~~A~~An FIX/FIXa mediated or associated process or event, or equivalently, an activity associated with plasma FIX/FIXa, according to the present invention is any event which requires the presence of FIX/IXa. The general mechanism of blood clot formation is reviewed by Ganong, in Review of Medical Physiology, 13th ed., Lange, Los Altos CA, pp411-414 (1987); Bach (1988) CRC Crit. Rev. Biochem. 23(4):~~359~~339-368 and Davie et al., (1991) Biochemistry 30:10363; and the rate of FIX in Limentoani et al., (1994) Hemostasis and Thrombosis Basic Principles and Clinical Practice, Third Edition, Coleman et al. Eds., Lippincott Company, Philadelphia. Coagulation requires the confluence of two processes, the production of thrombin which induces platelet aggregation and the formation of fibrin which renders the platelet plug stable. The process comprises several stages each requiring the presence of discrete proenzymes and procofactors. The process ends in fibrin crosslinking and thrombus formation. Fibrinogen is converted to fibrin by the action of thrombin. Thrombin, in turn, is formed by the proteolytic cleavage of prothrombin. This proteolysis is effected by FXa which binds to the surface of activated platelets and in the presence of FVa and calcium, cleaves prothrombin. TF-FVIIa is required for the proteolytic activation of FX by the extrinsic pathway of coagulation. FIX is activated by two different enzymes, FXIa (Fujeikawa et al., (1974) Biochemistry, 13:4508-4516; Di Scipio et al., (1978) J. Clin. Invest., 61:15268-1538; Østerud et al., (1978) J. Biol.. Chem. 253:5946-5951) and the tissue factor:factor VIIa (TF:FVIIa) complex (Østerud and ~~P~~Rapaport (1977) Proc. Natl. Acad. Sci. USA 74:5260-5264). The formed FIXa in complex with its cofactor FVIIIa assembles into the intrinsic Xase complex on cell surfaces such as platelets and endothelial cells, and converts substrate FX into FXa (Mann et al., (1992) Semin. Hematol.. 29:213-226). Thrombin generated by FXa enzymatic activity, cleaves fibrinogen leading to fibrin formation and also activates platelets resulting in platelet aggregation. Therefore, a process mediated by or associated with FIX/IXa, or an activity associated with FIXa includes any step in the coagulation cascade from the introduction of FIX in the extrinsic or intrinsic

pathway to the formation of a fibrin platelet clot and which initially involves the presence FIX/IXa. FIX/FIXa mediated or associated process, or FIXa activity, can be conveniently measured employing standard assays such as those described herein.

The paragraph beginning at page 21, line 25 has been amended as follows:

Further provided herein are an antibody or antibody fragment comprising any of the heavy chain CDR sequences as described above, and further comprising a light chain CDR amino acid sequence comprising the amino acid sequence of a light chain CDR amino acid sequence of Figure 2. By way of example, in one embodiment, the invention provides a single chain antibody fragment wherein any heavy chain comprising a CDR1 a CDR2 and a CDR3, and light chain (λc) comprising a λc-CDR1, a λc-CDR2 and a λc-CDR3 are contained in a single chain polypeptide species. By way of example and not limitation, the single chain antibody fragment is, in a particular embodiment, a scFv species comprising the heavy chain joined to the light chain by means of a flexible peptide linker sequence, wherein the heavy chain and light chain variable domains can associate in a "dimeric" structure analogous to that formed in a two-chain Fv species. In another embodiment, the single chain antibody fragment is a species comprising the heavy chain joined to the light chain by a linker that is too short to permit intramolecular pairing of the two variable domains, i.e., a single chain polypeptide monomer that forms a diabody upon dimerization with another monomer.

The paragraph beginning at page 26, line 26 has been amended as follows:

Another type of variant is an amino acid substitution variant. These variants have at least one amino acid residue in the antibody molecule removed and a different residue inserted in its place. The sites of greatest interest for substitutional mutagenesis include the hypervariable regions, but FR alterations are also contemplated. Conservative substitutions are shown in Table ~~1~~A under the heading of "preferred substitutions". If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions" in Table A, or as further described below in reference to amino acid classes, may be introduced and the products screened.

Table A beginning at page 27, line 3 has been amended as follows:

Table A

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val; leu; ile	val
Arg (R)	Lys; gln; asn	lys
Asn (N)	Gln; his; asp, lys; arg	gln
Asp (D)	Glu; asn	glu
Cys ~~(C)~~	Ser; ala	ser
Gln (Q)	Asn; glu	asn
Glu (E)	Asp; gln	asp
Gly (G)	Ala	ala
His (H)	Asn; gln; lys; arg	arg
Ile (I)	Leu; val; met; ala; phe; norleucine	leu
Leu (L)	Norleucine; ile; val; met; ala; phe	ile
Lys (K)	Arg; gln; asn	arg
Met (M)	Leu; phe; ile	leu
Phe (F)	Leu; val; ile; ala; tyr	tyr
Pro (P)	Ala	ala
Ser (S)	Thr	thr
Thr (T)	Ser	ser
Trp (W)	tyr; phe	tyr
Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

The paragraph beginning at page 47, line 12 and ending at page 48, line 2 has been amended as follows:

Antibody variants in which residues have been deleted, inserted, or substituted are recovered in the same fashion, taking account of any substantial changes in properties occasioned by the variation. For example, preparation of ~~a~~ an antibody fusion with another protein or polypeptide, e.g., a bacterial or viral antigen, facilitates purification; an immunoaffinity column containing antibody to the antigen can be used to adsorb the fusion polypeptide. Immunoaffinity columns such as a rabbit polyclonal anti-antibody column can be employed to absorb the antibody variant by binding it to at least one remaining immune epitope. Alternatively, the antibody may be purified by affinity chromatography using a purified FIX Gla domain-IgG coupled to a (preferably) immobilized resin such as AFFI-Gel 10 (Bio-Rad, Richmond, CA) or the like, by means well known in the art. A protease inhibitor such as phenyl methyl sulfonyl fluoride (PMSF) also may be useful to inhibit proteolytic degradation during

purification, and antibiotics may be included to prevent the growth of adventitious contaminants. One skilled in the art will appreciate that purification methods suitable for the native antibody may require modification to account for changes in the character of the antibody or its variants upon expression in recombinant cell culture.

The paragraph at page 65, lines 20-29 has been amended as follows:

Cross-species reactivity of 10C12 $F(ab')_2$ - The amino acid sequences of FIX-Gla domains of different animal species are much conserved (Fig. 1A), suggesting that an antibody that binds to human FIX-Gla may also recognize plasma FIX/IXa of various animals. The potency of 10C12 $F(ab')_2$ to inhibit the APTT in plasma from different species was therefore examined. As shown in Figure 9B, 10C12 $F(ab')_2$ most potently prolonged the APTT in dog and to a lesser extent ~~that~~than in rat and rabbit plasma. The specificity of the antibody effect towards FIX/IXa was evidenced by the absence of any effect on the PT in homologous plasma.

In the claims:

Claims 1-22 have been cancelled.

Claims 23-42 have been added.

23 (New). An isolated antibody or antigen binding fragment thereof which

(a) specifically binds a factor IX/IXa Gla domain; and

(b) comprises a heavy chain and a light chain variable region further wherein:

(i) the heavy chain variable region comprises a CDR1 which is SEQ ID NO:10, a CDR2 which is SEQ ID NO:11 and a CDR3 which is SEQ ID NO:12; and

(ii) the light chain variable region comprises an lcCDR1 which is SEQ ID NO:13, and lcCDR2 which is SEQ ID NO:14, and an lcCDR3 which is SEQ ID NO:15.

24 (New). A composition comprising the antibody or antigen binding fragment of Claim 23 and a carrier, excipient or stabilizer.

25 (New). The composition of Claim 24, wherein the carrier, excipient or stabilizer is pharmaceutically-acceptable.

26 (New). The composition of Claim 25, which is sterile.

27 (New). The composition of Claim 26 further comprising a thrombolytic agent.

28 (New). The composition of Claim 27 wherein the thrombolytic agent is tissue plasminogen activator.

29 (New). The composition of Claim 27 wherein the thrombolytic agent is streptokinase.

30 (New). The composition of Claim 27 wherein the thrombolytic agent is urokinase.

31 (New). The composition of Claim 27 wherein the thrombolytic agent is anisolated streptokinase plasminogen.

32 (New). The composition of Claim 26 which is lyophilized.

33 (New). The composition of Claim 26 which is liquid.

34 (New). The composition of Claim 27 which is lyophilized.

35 (New). The composition of Claim 27 which is liquid.

36 (New). An article of manufacture comprising;

(a) a container;
(b) a label on said container; and
(c) a composition comprising an antibody or antibody fragment of Claim 23 within said container;

wherein the composition is effective for treating a coagulation disorder, and optionally a label on said container indicating that the composition can be used for treating a coagulapathic disorder.

37 (New). An article of manufacture comprising:

(a) a container;

(b) a label on said container; and

(c) the composition of Claim 26 within said container;

wherein the composition is effective for treating a coagulation disorder, and optionally a label on said container indicating that the composition can be used for treating a coagulapathic disorder.

38 (New). An article of manufacture comprising:

(a) a container;

(b) a label on said container; and

(c) the composition of Claim 27 within said container;

wherein the composition is effective for treating a coagulation disorder, and optionally a label on said container indicating that the composition can be used for treating a coagulapathic disorder.

39 (New). An article of manufacture comprising:

(a) a container;

(b) a label on said container; and

(c) the composition of Claim 28 within said container;

wherein the composition is effective for treating a coagulation disorder, and optionally a label on said container indicating that the composition can be used for treating a coagulapathic disorder.

40 (New). An article of manufacture comprising:

(a) a container;

(b) a label on said container; and

(c) the composition of Claim 29 within said container;

wherein the composition is effective for treating a coagulation disorder, and optionally a label on said container indicating that the composition can be used for treating a coagulapathic disorder.

41 (New). An article of manufacture comprising:

(a) a container;

(b) a label on said container; and

(c) the composition of Claim 30 within said container;

wherein the composition is effective for treating a coagulation disorder, and optionally a label on said container indicating that the composition can be used for treating a coagulapathic disorder.

42 (New). An article of manufacture comprising:

(a) a container;

(b) a label on said container; and

(c) the composition of Claim 31 within said container;

wherein the composition is effective for treating a coagulation disorder, and optionally a label on said container indicating that the composition can be used for treating a coagulapathic disorder.